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10/709,880	06/03/2004	David M. Richlin	RICHP001US	9853

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EXAMINER

NOLAN, JASON MICHAEL

ART UNIT	PAPER NUMBER
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1626

NOTIFICATION DATE	DELIVERY MODE
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ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No. 10/709,880	Applicant(s) RICHLIN ET AL.	
	Examiner JASON M. NOLAN	Art Unit 1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 16 September 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-150 is/are pending in the application.
- 4a) Of the above claim(s) 2-150 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>11/23/09</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This Office Action is responsive to Applicant's Amendment – After Non-Final Rejection, filed September 16, 2009. As filed, Claims 1-150 are pending; of which, Claims 66-150 are withdrawn and Claims 1 & 66 are currently amended.

Information Disclosure Statement

Applicants' information disclosure statement (IDS), filed on November 23, 2009 has been considered. Please refer to Applicants' copy of the 1449 submitted herein.

Response to Amendment

Applicant's amendments with respect to Claims 1 & 66 have been fully considered and are entered. The 102-prior art rejection of Claim 1 over US 5,059,603 has been withdrawn per amendment. As amended, Claim 1 now recites therapeutic agents such as anesthetics, anti-inflammatory agents, and antiviral agents. Papaverine does not fall within those agents, so the rejection is withdrawn. The 102-prior art rejection of Claim 1 over US 7,273,887 has been withdrawn per amendment. As amended, Claim 1 is limited to a penetration enhancer selected from DMSO or lecithin and the '887 patent does not disclose the use of DMSO or lecithin.

Scope of Examined Claims

As pointed out in the previous Office Action (p. 5), if prior art is found that anticipates or renders obvious the Markush-type claim with respect to a non-elected

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species, the Markush-type claims shall be rejected and claims to the nonelected species held withdrawn from further consideration. For this reason, Claims 2-65 were objected to for containing non-elected subject matter (alternatively, they could have been withdrawn).

The rejections to Claim 1 have been withdrawn per amendment. For this reason, the search and examination of the Markush-type Claim 1 has been expanded. If prior art is found that anticipates or renders obvious the Markush-type claim with respect to a non-elected species, the Markush-type claims shall be rejected and claims to the nonelected species held withdrawn from further consideration.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claim 1 of the instant application is drawn to a preparation for topically delivering and localizing therapeutic agents. Said claim recites three components that are essential for the asserted utility: 1) a vasoconstrictor; 2) a penetration enhancer; and, 3) a therapeutic agent.

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Potter *et al.* (*Anesthesiology* 1946, 7, 499-504) in view of US 4,783,450 ("the '450 patent") when the penetration enhancer is lecithin and/or the abstract of Babar *et al.* (*Drug Development and Industrial Pharmacy* 1990, 16(3), 523-540) the penetration enhancer is dimethylsulfoxide (DMSO).

1. *Determining the scope and contents of the prior art –*

A) Vasoconstrictors and therapeutic agents: the "addition of a vasoconstrictor to a local anesthetic may have several beneficial effects: a decrease in the peak plasma concentration of the local anesthetic agent, increase in the duration and quality of anesthesia, reduction of the minimum concentration of anesthetic needed for nerve block, and decrease of blood loss during surgical procedures." A.L. Sisk *Anesth. Prog.* 1992, 39, 187-193, abstract. Epinephrine is the best studied and most widely used vasoconstrictor. *Id.* at 187. Potter *et al.* discloses that other vasoconstrictors, such as ephedrine, have been used with local anesthetics since at least 1946. Potter *et al.* discloses that vasoconstrictors decrease the flow of blood to that region and slow absorption of the anesthetic agent, thus prolonging its effect and decreasing its systemic toxicity (p. 499). Although Sisk and Potter *et al.* disclose injectable compositions containing local anesthetics and vasoconstrictors, the prior art of record

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(US 5,059,603 and US 7,273,887) has established that vasoconstrictors are also useful for topical applications. Thus, the prior art, taken as a whole, discloses that vasoconstrictors are useful (tolerated and beneficial) in combination with anesthetics for topical (or injectable) delivery of therapeutic agents.

B) Penetration enhancers and therapeutic agents: the topical delivery of therapeutic agents is a formidable challenge. "The greatest hindrance in the percutaneous delivery is the obstruction property of the stratum corneum, the outermost layer of the skin, in addition to the usual problems such as skin binding, skin metabolism, cutaneous toxicity and prolonged lag times." Ahad *et al. Exp. Opin. Ther. Patents* 2009, 19(7), 969-988, abstract. See also, H.A.E. Benson *Current Drug Delivery* 2005, 2, 23-33. The Ahad *et al.* publication states that there are about 150 different chemicals used by the pharmaceutical industry as penetration enhancers (p. 970). "To be ideal, penetration enhancers have to meet a set of qualitative criteria. These are: they must not be toxic non-irritant, non-allergenic and non-sensitizing to skin and they should be pharmacologically inert at the concentrations required to exert adequate permeation action. Their effect should be immediate, predictive and reversible."

As set forth above, there are a plethora of different penetration enhancers for one of skill in the art to choose from. It is noted, however, that "it is difficult to select rationally a penetration enhancer for a given permeant. Penetration enhancer potencies appear to be drug specific . . . the level of enhancement expected for these agents is unpredictable." Williams *et al. Advanced Drug Delivery Reviews* 2004, 56, 603-618, 615.

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The instant Claim 1 is limited to the selection of dimethyl sulfoxide (DMSO) or lecithin as the penetration enhancer. DMSO is known in the art for the delivery of non-steroidal, anti-inflammatory (NSAI) agents through the skin. See Abstract from Babar *et al.* (*Drug Development and Industrial Pharmacy* 1990, 16(3), 523-540). "DMSO is one of the earliest and most widely studied penetration enhancers . . . DMSO is used as a co-solvent in a vehicle for a commercial preparation of idoxuridine, used to treat severe herpetic infections of the skin, particularly those caused by herpes simplex. DMSO alone has also been applied topically to treat systemic inflammation." Williams at 607.

The US 4,783,450 patent discloses that lecithin is also known in the art for the delivery of analgesic agents through the skin (col. 2 Table, formulation number 5). Thus, the prior art, taken as a whole, discloses that penetration enhancers are useful (tolerated and beneficial) in combination with anesthetics for topical delivery of therapeutic agents.

C) Vasoconstrictors, penetration enhancers, and therapeutic agents: the prior art of record (US 5,059,603 and US 7,273,887) has established that vasoconstrictors are useful for topical applications in combination with penetration enhancers and therapeutic agents. Thus, the prior art, taken as a whole, discloses topical compositions comprising vasoconstrictors, penetration enhancers, and therapeutic agents.

2. Ascertaining the differences between the prior art and the claims at issue –

Potter *et al.* discloses injectable compositions comprising an anesthetic and a vasoconstrictor. Potter *et al.* does not disclose the use of a penetration enhancer for the topical delivery of such a solution. Babar *et al.* discloses compositions for topical delivery comprising DMSO and NSAI. Babar *et al.* does not disclose the use of a

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vasoconstrictor with said composition. The 4,783,450 patent discloses compositions for topical delivery comprising lecithin and analgesic agents. The 4,783,450 patent does not disclose the use of a vasoconstrictor with said composition.

3. *Resolving the level of ordinary skill in the pertinent art* – the level of ordinary skill in the art may be found by inquiring into: (1) the type of problems encountered in the art; (2) prior art solutions to those problems; (3) the rapidity with which innovations are made; (4) the sophistication of the technology; and (5) the education level of active workers in the field. *Custom Accessories, Inc.*, 807 F.2d at 962. All of those factors may not be present in every case, and one or more of them may predominate. *Envtl. Designs, Ltd. v. Union Oil Co.*, 713 F.2d 693, 696 (Fed.Cir.1983).

Based on the typical education level of active workers in the field of pharmaceuticals (chemistry, biology, biochemistry, etc.), as well as the high degree of sophistication required to solve problems encountered in the art, the Examiner finds that a person of ordinary skill in the art would have at least a college degree in a field required for the pharmaceutical arts and at least four years of work experience, i.e. a masters or doctorate level scientist.

4. *Considering objective evidence present in the application indicating obviousness or nonobviousness* – none.

Conclusion – in view of the high level of skill in the art, an artisan in this field would be motivated to combine the cumulative disclosures of the prior art to arrive at a topical composition comprising a vasoconstrictor, a penetration enhancer, and a therapeutic agent (see, e.g., US 5,059,603 and US 7,273,887). The instant claim

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recites some of the most studied and widely used vasoconstrictors in the art. Further, the instant claim recites DMSO and lecithin - penetration enhancers are widely known in the art. The scope of therapeutic agents includes the classes of agents most widely utilized for topical delivery, such as analgesic agents NSAID, and antiviral agents. See, e.g., Brandao *et al.* Chapter 35 from Contact Dermatitis, Springer Berlin Heidelberg (Publisher), 4th Ed., 2006, Frosch, Menne, & Lepoittevin (Editors).

Therefore, one of ordinary skill in the art would be motivated to combine the disclosures of Potter *et al.* and either US 4,783,450 or Babar *et al.* to arrive at the instant claimed invention with an expectation of success. When considering the prior art as a whole, one of ordinary skill in the art would reach the conclusion that the instant claim lacks an inventive concept and are prima facie obvious.

The Supreme Court stated: "When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." *KSR International Co. v. Teleflex Inc.*, USPQ2d, 1385, 1398 (2007); 127 SCt 1727; 167 Led2d 705; 550 US 398. In this case, the use of vasoconstrictors and penetration enhancers in combination with therapeutic agents for topical delivery are known options within the technical grasp of one of ordinary skill in the art. The Court further commented: "If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103." *Id.* In this case, the combination of therapeutic agents, vasoconstrictors and penetration

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enhancers has been successfully demonstrated in the prior art (*supra*). However, it was noted above that the selection of a penetration enhancers for particular therapeutic agents is unpredictable. Claim 1 is not drawn to particular therapeutic agents. For this reason, the Examiner suggests for Applicant to amend the generic language in the Markush-type Claim 1 to recite specific therapeutic agents. Due to the unpredictable nature of the penetration enhancers, claims drawn to topical compositions comprising *particular* therapeutic agents (i.e., species such as ketoprofen), *particular* penetration enhancers (i.e., DMSO or lecithin), and *particular* vasoconstrictors (i.e., phenylephrine) will have objective indications of non-obviousness.

Conclusion

No claims are allowed. Claims 2-150 are withdrawn.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

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the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jason M. Nolan whose telephone number is (571) 272-4356 and e-mail is Jason.Nolan@uspto.gov. The examiner can normally be reached on Mon - Fri (9:00 - 5:30PM). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph M^cKane can be reached on (571) 272-0699. The USPTO fax number for applications is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system, (either Private PAIR or Public PAIR). Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. For questions on Private PAIR system, contact the Electronic Business Center at (866) 217-9197.

/Jason M. Nolan/

Examiner, Art Unit 1626

/Rebecca L Anderson/

Primary Examiner, Art Unit 1626